

Supplementary data

DrugScore^{PPI} webserver:

**Fast and accurate *in silico* alanine scanning for scoring
protein-protein interactions**

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Table S1: Alanine scanning dataset used for training^[a]

PDB code	Mutated partner	Residue number	Amino acid ^[b]	$\Delta\Delta G_{\text{exp}}$ ^[c]	$\Delta\Delta G_{\text{calc}}$ ^[d]
1A22	hGH	21	H	0.2	0.48
1A22	hGH	22	Q	-0.2	0.22
1A22	hGH	25	F	-0.4	0.83
1A22	hGH	45	L	1.2	0.87
1A22	hGH	46	Q	0.1	0.38
1A22	hGH	56	E	0.4	0.66
1A22	hGH	62	S	0.1	0.46
1A22	hGH	63	N	0.3	0.61
1A22	hGH	64	R	1.6	3.21
1A22	hGH	65	E	-0.5	0.49
1A22	hGH	68	Q	0.6	0.87
1A22	hGH	164	Y	0.3	0.53
1A22	hGH	167	R	0.3	0.48
1A22	hGH	168	K	-0.2	1.03
1A22	hGH	171	D	0.8	1.45
1A22	hGH	172	K	2	1.02
1A22	hGH	174	E	-0.9	0.58
1A22	hGH	175	T	2	0.65
1A22	hGH	176	F	1.9	0.49
1A22	hGH	178	R	2.4	1.02
1A22	hGH	179	I	0.8	1.63
1A22	hGHbp	243	R	2.12	1.11
1A22	hGHbp	244	E	1.69	0.52
1A22	hGHbp	271	R	0.54	1.04
1A22	hGHbp	275	E	-0.1	0.26
1A22	hGHbp	276	W	0.51	2.33
1A22	hGHbp	298	S	-0.05	0.36
1A22	hGHbp	302	S	-0.2	0.64
1A22	hGHbp	303	I	1.61	0.89
1A22	hGHbp	305	I	1.94	0.69
1A22	hGHbp	320	E	-0.19	0.53
1A22	hGHbp	321	K	0.08	0.37
1A22	hGHbp	324	S	0.28	0.55
1A22	hGHbp	326	D	0.99	0.61
1A22	hGHbp	327	E	0.97	0.66
1A22	hGHbp	364	D	1.49	1.46
1A22	hGHbp	365	I	2.13	0.42
1A22	hGHbp	366	Q	0.02	0.10
1A22	hGHbp	367	K	-0.02	0.79
1A22	hGHbp	371	V	-0.64	0.74
1A22	hGHbp	416	Q	0.89	0.39
1A22	hGHbp	417	R	0.28	-0.18
1A22	hGHbp	418	N	0.3	0.91
1A22	hGHbp	419	S	0.03	0.55
1A22	hGHbp	301	T	1.76	0.53
1A4Y	Rnase Inh	261	W	0.1	0.77
1A4Y	Rnase Inh	263	W	1.2	2.15
1A4Y	Rnase Inh	289	S	0	0.51
1A4Y	Rnase Inh	318	W	1.5	2.01
1A4Y	Rnase Inh	320	K	-0.3	0.69
1A4Y	Rnase Inh	344	E	0.2	0.59
1A4Y	Rnase Inh	375	W	1	1.66

1A4Y	Rnase Inh	401	E	0.9	0.62
1A4Y	Rnase Inh	434	Y	3.3	3.41
1A4Y	Rnase Inh	435	D	3.5	3.82
1A4Y	Rnase Inh	437	Y	0.8	2.61
1A4Y	Rnase Inh	459	I	0.7	0.64
1A4Y	Angiogenin	5	R	2.3	2.03
1A4Y	Angiogenin	8	H	0.9	0.53
1A4Y	Angiogenin	12	Q	0.3	0.68
1A4Y	Angiogenin	13	H	-0.3	0.45
1A4Y	Angiogenin	31	R	0.2	0.94
1A4Y	Angiogenin	32	R	0.9	1.35
1A4Y	Angiogenin	68	N	0.2	0.41
1A4Y	Angiogenin	84	H	0.2	0.55
1A4Y	Angiogenin	89	W	0.2	1.59
1A4Y	Angiogenin	108	E	-0.3	0.73
1A4Y	Angiogenin	114	H	0.65	0.53
1AHW	TF	167	T	0	0.35
1AHW	TF	170	T	1	0.47
1AHW	TF	176	L	1	0.36
1AHW	TF	178	D	-0.5	0.49
1AHW	TF	197	T	1.3	0.34
1AHW	TF	198	V	-0.3	0.47
1AHW	TF	199	N	1.1	0.45
1AIE	P53	352	D	0.55	0.89
1AIE	P53	326	E	0.4	-0.09
1AIE	P53	336	E	-0.75	0.31
1AIE	P53	339	E	0.45	0.40
1AIE	P53	343	E	0.28	0.26
1AIE	P53	346	E	0.1	0.34
1AIE	P53	349	E	0.95	0.56
1AIE	P53	328	F	1.8	1.02
1AIE	P53	338	F	1.8	1.05
1AIE	P53	351	K	-0.62	1.16
1AIE	P53	350	L	0.53	1.09
1AIE	P53	340	M	1.6	0.46
1AIE	P53	345	N	0.93	1.84
1AIE	P53	331	Q	0.35	0.06
1AIE	P53	333	R	0.97	0.64
1AIE	P53	335	R	0.53	0.75
1AIE	P53	337	R	2.33	1.57
1AIE	P53	342	R	0.35	0.69
1AIE	P53	329	T	0.9	0.42
1BRS	Barnase	54	D	-0.8	0.35
1BRS	Barnase	59	R	5.2	2.93
1BRS	Barnase	60	E	-0.2	0.81
1BRS	Barnase	73	E	2.8	0.56
1BRS	Barstar	29	Y	3.4	5.03
1BRS	Barstar	35	D	4.5	3.70
1BRS	Barstar	42	T	1.8	0.49
1BRS	Barstar	76	E	1.3	0.54
1BRS	Barstar	80	E	0.5	0.37
1BXI	Im9	23	C	0.92	0.38
1BXI	Im9	24	N	0.14	0.02
1BXI	Im9	26	D	0.34	0.31
1BXI	Im9	27	T	0.73	0.57
1BXI	Im9	28	S	0.17	0.40

1BXI	Im9	29	S	0.96	0.47
1BXI	Im9	30	E	1.41	0.80
1BXI	Im9	33	L	3.42	0.96
1BXI	Im9	34	V	2.58	0.90
1BXI	Im9	37	V	1.66	1.03
1BXI	Im9	38	T	0.9	0.55
1BXI	Im9	41	E	2.08	0.69
1BXI	Im9	48	S	0.01	0.36
1BXI	Im9	50	S	2.19	0.57
1BXI	Im9	53	I	0.85	0.59
1BXI	Im9	54	Y	4.83	4.04
1BXI	Im9	55	Y	4.63	4.48
1CBW	BPTI	11	T	0.2	0.53
1CBW	BPTI	15	K	2	2.17
1CBW	BPTI	17	R	0.5	1.11
1CBW	BPTI	19	I	0.1	0.99
1CBW	BPTI	34	V	0	0.44
1CBW	BPTI	39	R	0.2	0.93
1DAN	TF	17	T	0.1	0.45
1DAN	TF	18	N	0.2	0.79
1DAN	TF	20	K	2.6	1.34
1DAN	TF	21	T	-0.2	0.42
1DAN	TF	22	I	0.7	1.34
1DAN	TF	24	E	0.7	0.57
1DAN	TF	37	Q	0.55	0.96
1DAN	TF	41	K	0.35	0.35
1DAN	TF	42	S	-0.1	0.28
1DAN	TF	44	D	0.7	2.23
1DAN	TF	46	K	0.25	0.69
1DAN	TF	47	S	0.05	0.39
1DAN	TF	48	K	0.4	0.62
1DAN	TF	50	F	0.4	1.44
1DAN	TF	58	D	2.18	2.21
1DAN	TF	68	K	-0.1	0.33
1DAN	TF	99	E	-0.2	0.37
1DAN	TF	128	E	0.1	0.46
1DAN	TF	133	L	0	1.22
1DAN	TF	135	R	0.55	1.17
1DAN	TF	140	F	1.5	0.81
1DAN	TF	163	S	0	0.40
1DAN	TF	203	T	0.1	0.43
1DAN	TF	207	V	-0.2	1.42
1DAN	TF	208	E	0	0.45
1DFJ	Rnase Inh	202	E	1	0.55
1DFJ	Rnase Inh	257	W	1.3	1.30
1DFJ	Rnase Inh	259	W	2.2	2.01
1DFJ	Rnase Inh	283	E	1.3	0.41
1DFJ	Rnase Inh	285	S	0.8	0.39
1DFJ	Rnase Inh	314	W	1	0.76
1DFJ	Rnase Inh	316	K	1.3	0.48
1DFJ	Rnase Inh	397	E	1.3	0.62
1DFJ	Rnase Inh	453	R	0.8	0.49
1DFJ	Rnase Inh	455	I	0.3	1.06
1DFJ	Rnase Inh	430	Y	5.9	4.50
1DFJ	Rnase Inh	431	D	3.6	2.45
1DFJ	Rnase Inh	433	Y	2.6	2.38

1DVF	D1.3	H30	T	0.9	0.45
1DVF	D1.3	H32	Y	1.8	0.01
1DVF	D1.3	H52	W	4.2	2.89
1DVF	D1.3	H54	D	4.3	3.46
1DVF	D1.3	H56	N	1.2	1.53
1DVF	D1.3	H58	D	1.6	0.82
1DVF	D1.3	H99	R	1.9	0.23
1DVF	D1.3	H100	D	2.8	1.16
1DVF	D1.3	L30	H	1.7	0.44
1DVF	D1.3	L32	Y	2	1.47
1DVF	D1.3	L49	Y	1.7	0.77
1DVF	D1.3	L50	Y	0.7	1.04
1DVF	D1.3	L92	W	0.3	1.16
1DVF	D1.3	L93	S	1.2	0.42
1DVF	E5.2	30	K	1	0.33
1DVF	E5.2	33	H	1.9	0.62
1DVF	E5.2	52	D	1.7	1.03
1DVF	E5.2	54	N	1.9	1.25
1DVF	E5.2	97	I	2.7	1.81
1DVF	E5.2	98	Y	4.7	4.58
1DVF	E5.2	100	Q	1.6	1.68
1DVF	E5.2	49	Y	1.9	1.12
1F47	FTSZ fragm.	4	D	0.7	0.00
1F47	FTSZ fragm.	5	Y	0.9	2.35
1F47	FTSZ fragm.	6	L	0.9	1.70
1F47	FTSZ fragm.	7	D	1.8	0.89
1F47	FTSZ fragm.	8	I	2.5	1.74
1F47	FTSZ fragm.	11	F	2.5	1.11
1F47	FTSZ fragm.	12	L	2.3	1.05
1F47	FTSZ fragm.	14	K	0	0.42
1F47	FTSZ fragm.	15	Q	0	0.19
1FCC	Protein G	25	T	0.24	0.43
1FCC	Protein G	28	K	1.3	1.55
1FCC	Protein G	31	K	3.5	1.10
1FCC	Protein G	35	N	2.4	2.45
1FCC	Protein G	40	D	0.3	0.94
1FCC	Protein G	42	E	0.4	0.52
1FCC	Protein G	43	W	3.8	1.56
1GC1	CD4	23	S	0.29	0.47
1GC1	CD4	25	Q	0.03	0.41
1GC1	CD4	27	H	0.28	0.51
1GC1	CD4	29	K	0.59	0.99
1GC1	CD4	31	S	0.1	0.46
1GC1	CD4	32	N	0.18	0.11
1GC1	CD4	33	Q	0.1	0.21
1GC1	CD4	35	K	0.32	1.42
1GC1	CD4	40	Q	-0.41	0.45
1GC1	CD4	42	S	0	0.59
1GC1	CD4	44	L	1.04	0.51
1GC1	CD4	45	T	-0.15	0.50
1GC1	CD4	52	N	0.7	1.07
1GC1	CD4	56	D	-0.07	0.42
1GC1	CD4	59	R	1.16	0.59
1GC1	CD4	60	S	-0.09	0.28
1GC1	CD4	63	D	-0.32	1.07
1GC1	CD4	64	Q	0.44	0.76

1IAR	IL4	19	E	-0.32	0.40
1IAR	IL4	82	F	-0.08	0.53
1IAR	IL4	11	I	0.07	0.41
1IAR	IL4	5	I	1.17	1.66
1IAR	IL4	77	K	0.15	0.37
1IAR	IL4	84	K	0.35	0.42
1IAR	IL4	15	N	-0.03	0.42
1IAR	IL4	89	N	1.56	1.91
1IAR	IL4	78	Q	0.13	0.50
1IAR	IL4	8	Q	-0.02	0.38
1IAR	IL4	81	R	0.48	1.16
1IAR	IL4	85	R	0.43	1.09
1IAR	IL4	88	R	3.75	1.79
1IAR	IL4	16	S	-0.18	0.41
1IAR	IL4	13	T	0.98	0.53
1IAR	IL4	6	T	-0.1	0.62
1JCK	SEC3	20	T	1.4	0.60
1JCK	SEC3	26	Y	1.7	1.92
1JCK	SEC3	60	N	1.3	1.08
1JCK	SEC3	91	V	2.1	1.58
1JCK	SEC3	103	K	0.4	0.44
1JCK	SEC3	176	F	1.9	0.60
1JRH	A6	L27	E	0.54	0.43
1JRH	A6	L28	D	0.44	0.54
1JRH	A6	L30	Y	1.1	1.62
1JRH	A6	L91	Y	0.58	0.91
1JRH	A6	L92	W	2.8	2.75
1JRH	A6	L93	S	-0.65	0.43
1JRH	A6	L94	T	0.38	0.51
1JRH	A6	L96	W	1.7	0.82
1JRH	A6	H32	Y	1.4	1.85
1JRH	A6	H52	W	2.7	1.60
1JRH	A6	H53	W	2.4	0.67
1JRH	A6	H54	D	1.9	1.12
1JRH	A6	H56	D	1.8	0.91
1JRH	A6	H58	Y	1.2	2.54
1JRH	A6	H95	R	0.54	0.37
1JRH	Interferon	48	N	-0.3	0.48
1JRH	Interferon	51	V	1.9	1.57
1JRH	Interferon	52	K	3	1.81
1JRH	Interferon	53	N	3.9	2.84
1JRH	Interferon	54	S	0.3	0.43
1JRH	Interferon	79	N	-0.4	0.65
1JRH	Interferon	84	R	-0.3	0.28
1JRH	Interferon	98	K	0	0.83
1VFB	D1.3	L30	H	0.8	0.52
1VFB	D1.3	L32	Y	1.3	2.17
1VFB	D1.3	L49	Y	0.8	1.28
1VFB	D1.3	L50	Y	0.4	1.80
1VFB	D1.3	L53	T	-0.23	0.54
1VFB	D1.3	L92	W	1.71	1.34
1VFB	D1.3	L93	S	0.11	0.37
1VFB	D1.3	H30	T	0.09	0.42
1VFB	D1.3	H32	Y	0.5	0.99
1VFB	D1.3	H52	W	1.23	1.59
1VFB	D1.3	H99	R	0.47	0.00

1VFB	D1.3	H100	D	3.1	3.61
1VFB	HEL	18	D	0.3	1.85
1VFB	HEL	19	N	0.3	1.39
1VFB	HEL	23	Y	0.4	0.41
1VFB	HEL	24	S	0.8	0.51
1VFB	HEL	116	K	0.7	0.95
1VFB	HEL	118	T	0.8	0.38
1VFB	HEL	119	D	1	1.56
1VFB	HEL	120	V	0.9	0.85
1VFB	HEL	121	Q	2.9	1.95
1VFB	HEL	124	I	1.2	0.73
1VFB	HEL	125	R	1.8	2.19
1VFB	HEL	129	L	0.2	0.41
3HFM	HYHEL-10	L50	Y	4.6	3.28
3HFM	HYHEL-10	L53	Q	1	0.49
3HFM	HYHEL-10	L96	Y	2.8	1.37
3HFM	HYHEL-10	H31	S	0.2	0.53
3HFM	HYHEL-10	H32	D	2	0.77
3HFM	HYHEL-10	H33	Y	6	4.95
3HFM	HYHEL-10	H53	Y	3.29	2.75
3HFM	HYHEL-10	H58	Y	1.7	3.09
3HFM	HEL	15	H	-0.5	0.23
3HFM	HEL	20	Y	5	2.84
3HFM	HEL	21	R	1	1.93
3HFM	HEL	63	W	0.3	0.73
3HFM	HEL	73	R	-0.2	1.07
3HFM	HEL	75	L	1.25	1.04
3HFM	HEL	89	T	0	0.58
3HFM	HEL	93	N	0.6	0.97
3HFM	HEL	98	I	-0.1	0.50
3HFM	HEL	100	S	0.25	0.58
3HFM	HEL	101	D	1.50	1.77

[a] 309 protein-protein interface alanine mutations derived from the Alanine Scanning Energetics Database (ASEdb).¹

[b] One letter code.

[c] Experimental $\Delta\Delta G$ values for wildtype-to-Ala mutations in kcal mol⁻¹ derived from ASEdb.

[d] $\Delta\Delta G$ values in kcal mol⁻¹ computed by adapted Drugscore^{PPI} potentials.

Table S2: External Ras/RalGDS test set^[a]

PDB code	Mutated partner	Residue number ^[b]	Amino acid ^[c]	$\Delta\Delta G_{exp}$ ^[d]	$\Delta\Delta G_{calc}$ ^[e]
1LFD	RalGDS-RBD	14	I	1.45	1.01
1LFD	RalGDS-RBD	16	R	2.30	0.51
1LFD	RalGDS-RBD	23	N	0.95	-0.31
1LFD	RalGDS-RBD	25	N	0.50	1.03
1LFD	RalGDS-RBD	27	Y	3.60	3.16
1LFD	RalGDS-RBD	28	K	2.50	0.83
1LFD	RalGDS-RBD	29	S	0.95	0.47
1LFD	RalGDS-RBD	44	K	0.45	1.27
1LFD	RalGDS-RBD	47	D	-0.30	0.2
1LFD	RalGDS-RBD	48	K	2.80	0.87
1LFD	RalGDS-RBD	52	E	-0.20	0.47
1LFD	Ras	25	Q	0.90	0.19
1LFD	Ras	29	V	0.50	0.06
1LFD	Ras	31	E	0.25	0.47
1LFD	Ras	33	D	1.10	1.83
1LFD	Ras	37	E	1.20	-0.32
1LFD	Ras	38	D	3.90	2.62
1LFD	Ras	39	S	-0.75	0.23
1LFD	Ras	40	Y	3.70	1.23
1LFD	Ras	41	R	0.85	0.81
1LFD	Ras	62	E	0.20	0.03
1LFD	Ras	63	E	0.10	0.24

^[a] 22 alanine mutations in the Ras/RalGDS interface derived from Kiel *et al.*²

^[b] Numbering according to Vetter *et al.*³

^[c] One letter code.

^[d] Experimental $\Delta\Delta G$ values in kcal mol⁻¹ derived from Kiel *et al.*²

^[e] $\Delta\Delta G$ values in kcal mol⁻¹ computed by adapted DrugScore^{PPI} potentials.

Table S3: Weighting coefficients according to eq. 2

Coefficient ^[a]	Value ^[b]
<i>c_{T(r)}</i>	
Val_C.3	-19.40
Leu_C.3	-12.78
Ile_C.3	-21.92
Trp_C.2	-30.73
Asn_N.am	-28.89
Gln_C.2	-49.04
Gln_O.2	4.43
Gln_N.am	20.35
Tyr_C.3	28.19
Tyr_C.ar	-27.73
Asp_C.3	-48.80
Asp_C.2	90.97
Asp_O.co2	-72.96
Glu_C.2	24.25
Glu_O.co2	-19.57
His_C.2	2.56
Lys_C.3	-10.15
Arg_C.3	-24.39
Arg_C.cat	-112.79
Arg_N.pl3	38.07
Backbone_C.2	-10.59
Backbone_O.2	-35.13
Backbone_N.am ^[c]	-7.85
<i>s</i>	
Met_C.3	
Met_S.3	
Phe_C.3	
Phe_C.ar	
Cys_C.3	
Cys_S.3	
His_C.3	
Trp_C.3	
Trp_C.ar	
Ser_C.3	
Ser.O.3	-6.30
Thr_C.3	
Thr_O.3	
Asn_C.3	
Asn_C.2	
Asn_O.2	
Gln_C.3	
Tyr_O.3	
Glu_C.3	
Lys_N.3	
Backbone_C.3	
<i>k</i>	
<i>a</i>	0.03
<i>a</i>	0.89

^[a] Amino acid three letter code (except for ‘Backbone’) followed by Tripos mol2 type descriptor.

^[b] In 10^6 kcal mol⁻¹.

^[c] This includes Trp_N.am and His_N.am for the sidechain nitrogen atoms of Trp and His, respectively. Following the Tripos mol2 type definition, Trp_N.pl3 and His_N.pl3 would have been chosen. However,

because these residues form H-bonds in the majority of the cases and not salt-bridges, the N.pl3 atomtype was reserved for Arg and replaced by N.am in Trp and His.

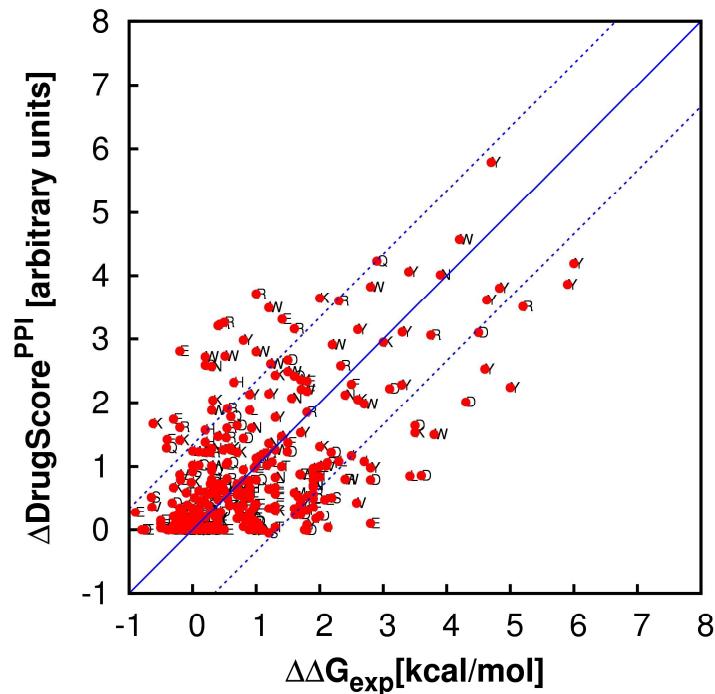


Figure S1: Calculated $\Delta\Delta G$ values using original DrugScore^{PPI} pair potentials versus experimentally determined $\Delta\Delta G$ values for the alanine scanning dataset (Table S1): $r = 0.58$, $\text{STD} = 1.06 \text{ kcal mol}^{-1}$, $p\text{-value} < 0.05$, $F = 158.48$, $N = 309$.

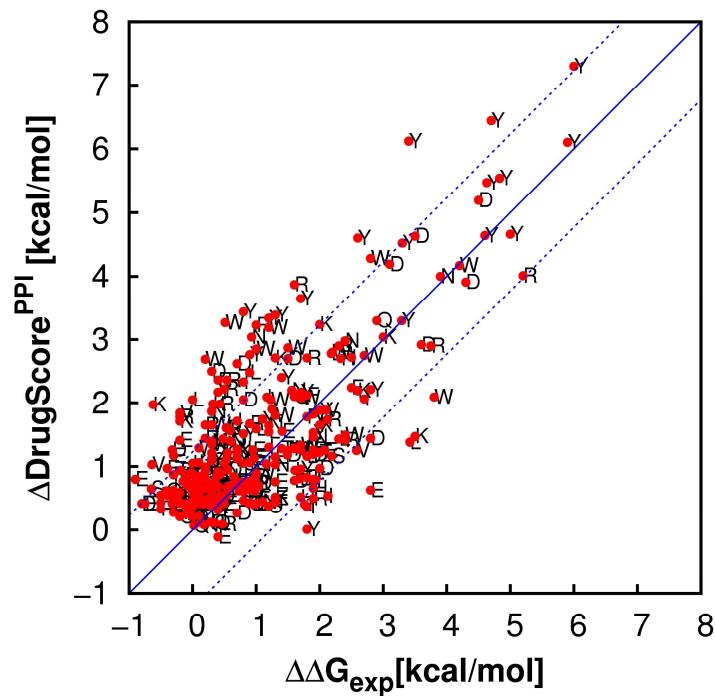


Figure S2: Calculated $\Delta\Delta G$ values using adapted DrugScore^{PPI} potentials versus experimentally determined $\Delta\Delta G$ values for the alanine scanning dataset (Table S1): $r_{\text{train}} = 0.73$, $\text{STD} = 0.84 \text{ kcal mol}^{-1}$, $p\text{-value} < 0.05$, $F = 345.16$, $N = 309$.

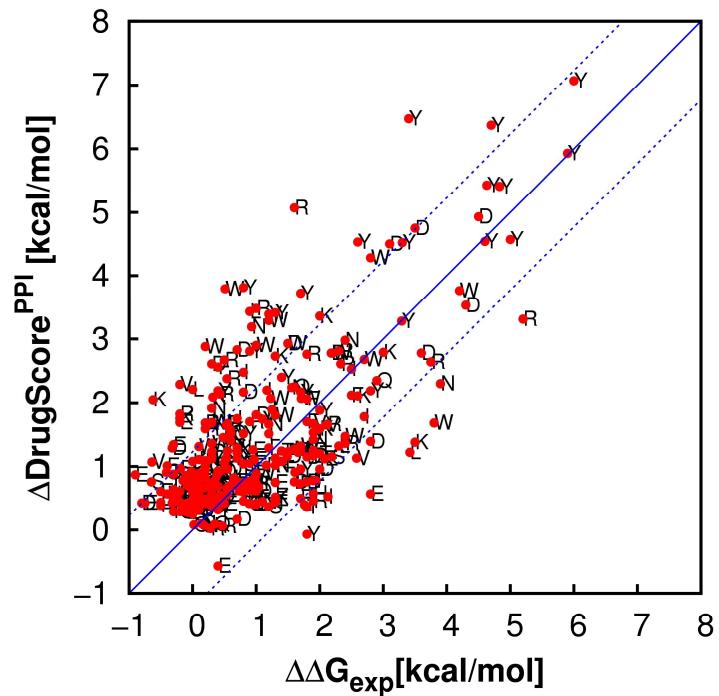


Figure S3: Calculated $\Delta\Delta G$ values obtained by leave-one-mutation-out cross-validation using adapted DrugScore^{PPI} potentials versus experimentally determined $\Delta\Delta G$ values for the alanine scanning dataset (Table S1). $r_{\text{LOO}} = 0.64$, $STD = 0.94 \text{ kcal mol}^{-1}$, $N = 309$.

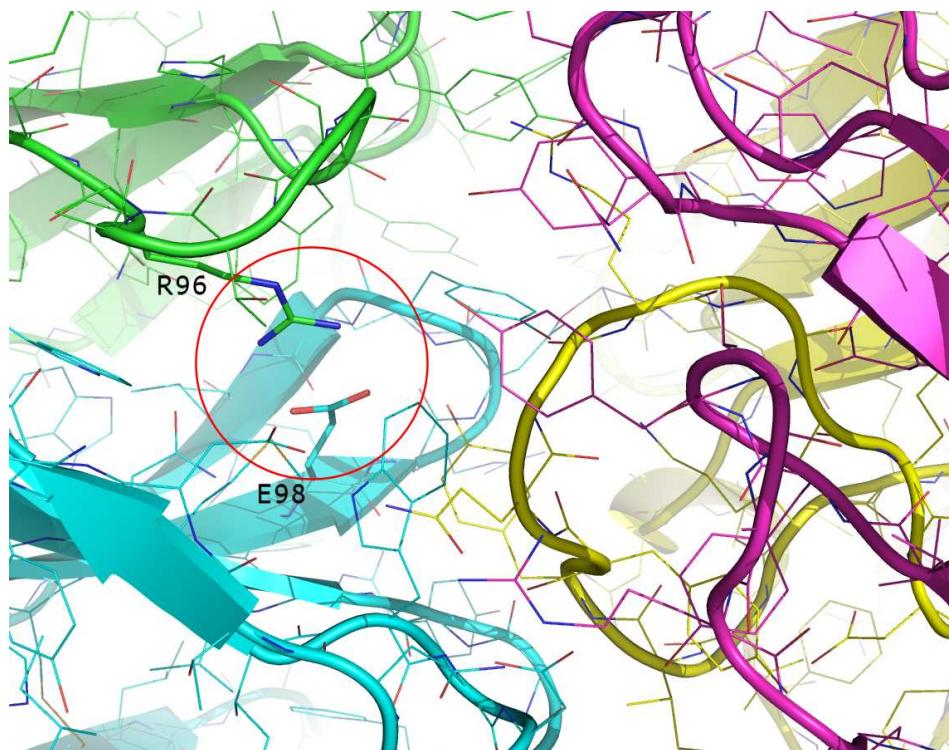


Figure S4: Example for mutations not included in the dataset of 309 alanine mutations. Close to the protein-protein interface of PDB entry 1DVF, formed by fragments from antibodies D1.3 (chain A: green; chain B: cyan) and E5.2 (chain C :magenta; chain D: yellow), residues R96 on chain A and E98 on chain B form an intramolecular saltbridge. $\Delta\Delta G$ values associated with the alanine mutations of these residues will very likely report on the stabilization or destabilization of the structure of D1.3 rather than on changes in the interactions with E5.2.

References

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